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ORIGINAL ARTICLE

# Nitrosylation of imidazo[1,2-*a*]pyridines in metal free system

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tert-Butyl nitrite (TBN);
Near quantitative yields

**Abstract** An efficient nitrosylation of imidazo[1,2-*a*]pyridines has been developed using tert-Butyl nitrite (TBN) as the NO resource. The nitrosylation protocol demonstrates broad compatibilities, with various functional groups such as halogen, Me, OMe, COOMe et al. well tolerated. Near quantitative yields could be obtained within the imidazo[1,2-*a*]pyridine scaffold under the optimized conditions.



## 1. Introduction

In recent years, C–H activation has emerged as a powerful strategy for the construction of various small molecules and pharmaceutical intermediates. However, the current protocol focused on the precious metal catalyst, including Pd, Rh, and Ir salts [1]. Alternatively, earth-abundant first-row transition-metal such as Fe, Co, and Ni served as potential replacements with the advancement of synthetic methodology and technology [2]. However, there is still a great need to develop environmentally benign, operationally convenient and green protocol without the aid of metal catalysis [3]. Meanwhile, imidazo[1,2-*a*]pyridine derivatives have been extensively investigated owing to their pharmaceutical and biological applications [4–6]. Many commercialized drugs containing imidazo[1,2-*a*]pyridine skeleton [7,8], such as alpidem, saripidem and zolpidem et al., have been developed (Fig. 1) [9–15]. The biological activities of imidazo[1,2-*a*]pyridine are dependent on different substituents at its framework. In this context, our group has been interested in exploring new methodologies with regard to established imidazo[1,2-*a*]pyridine derivatives [16–18]. In 2015, we described a Rh(III)-catalyzed annulation of 2-arylimidazo[1,2-*a*]pyridines and alkynes via direct double C–H activation [16]. To avoid the use of catalytic amount of metal catalysis, catalyst-free Friedel–Crafts hydroxyalkylation [17] and alkylation [18] of imidazo[1,2-*a*]pyridine were also reported. Among the imidazo[1,2-*a*]pyridine derivants, 3-nitrosoimidazo[1,2-*a*]-pyridine complexes have received wide attention for their

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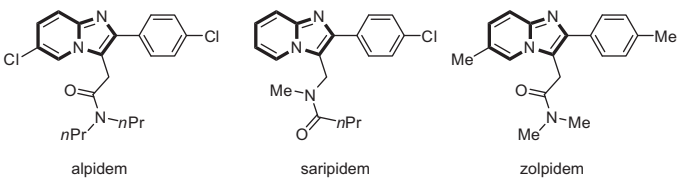



**Figure 1** Imidazo[1,2-*a*]pyridine as the framework in drugs.

antiretroviral activities [19]. Although numerous literatures for the direct C3 nitrosylation of imidazo[1,2-*a*]pyridine frameworks have been reported [20–22], most of them adopted $HNO_3$ or $HNO_2$ as the NO source. In order to avoid the acidic and harsh conditions, the development of general and efficient methods for the nitrosylation of imidazo[1,2-*a*]pyridine is highly desirable. Herein, we reported a straightforward and general route for the synthesis of 3-nitrosoimidazo[1,2-*a*]pyridines.

## 2. Methods

### 2.1. Materials

2-Phenylimidazo[1,2-*a*]pyridines were prepared according to previous literature [23]. All other chemicals including Pd $(OAc)_2$, $RhCl_3$, and $NiCl_2$, as well as NO sources ($AgNO_2$, $NaNO_2$, and TBN) were used as purchased without purification unless otherwise stated. The solvent employed to the reaction was dried and freshly distilled before use.

### 2.2. Instrumentation

$^1H$ and $^{13}C$ NMR spectra were all recorded on a Bruker DPX 400 instrument using TMS as an internal standard. Data are reported as follows: chemical shift ($\delta$ ppm), multiplicity ($s$ = single, $d$ = doublet, $t$ = triplet, $q$ = quartet, $m$ = multiplet), integration, and coupling constants in Hertz (Hz). Melting points were measured on a WC-1 instrument and were uncorrected. HRMS was determined on a *Waters* Q-Tof Micro MS/MS System ESI spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh).

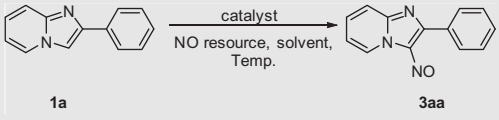
### 2.3. General procedure for the synthesis of 3-nitroso-2-phenylimidazo[1,2-a]pyridine

In a 10 mL vial were added the requisite 2-arylimidazo[1,2-*a*]pyridine derivatives (1.0 eq.), TBN (2.0 eq.) and DCE (1 mL). The reaction vial was sealed and heated to 90 °C for 30 min. After cooling to room temperature, the product was isolated through silica gel chromatography using $CH_2Cl_2$ as an eluent to afford the desired product.

## 3. Results and discussion

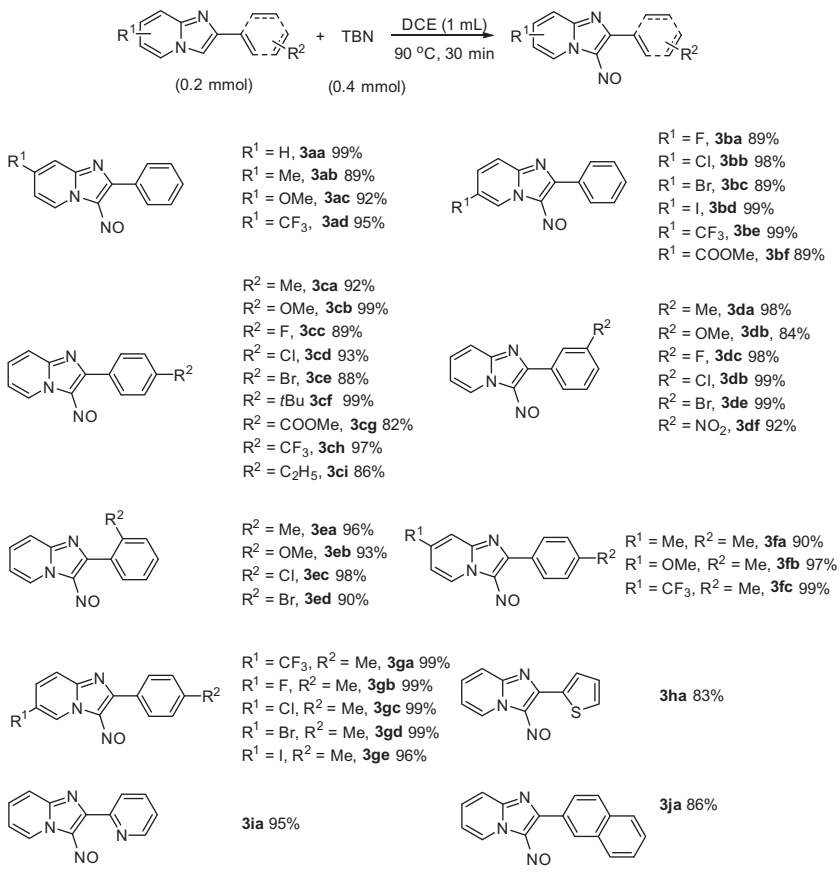
Initially, we speculated that the nitrosylation of imidazo[1,2-*a*]pyridine at C3 position would require metal as the catalyst via C–H functionalization. Based on this hypothesis, several metal catalysts have been applied into the reaction. $Pd(OAc)_2$ was tested firstly owing to its outstanding catalytic activities in C–H activation. However, no target product was obtained under the setting reaction conditions (Table 1, entry 1). Subsequently, $RhCl_3$ and $NiCl_2$ were also introduced into the nitrosylation reaction, respectively (Table 1, entry 2–3). However, there was still no desired product obtained. Using $AgNO_2$ as the NO source instead of $NaNO_2$ could achieve slightly better yield (Table 1, entry 4). In view of above unsatisfied results, we attempted to explore the reaction in the presence of other NO source. As the nitrosylation reagent, TBN has been reported in homogeneous catalytic system to successfully access oxindoles and quinoxaline N-oxides [24,25]. We were interested in investigating TBN initialized nitrosylation of imidazo[1,2-*a*]pyridine derivants. To our delight, a moderate yield was achieved using a mixture of palladium salts and TBN (Table 1, entry 5). Unexpectedly, the yield could reach up to 99% yield in the absence of metal salts in 2 h (Table 1, entry 6). The excellent result could be still reproduced in 0.5 h (Table 1, entry 7), indicating that the reaction could proceed smoothly in the metal free system. With preliminary data in hand, a variety of solvents were screened. As can be

**Table 1** Screening of the nitrosylation reaction conditions.




| Entry[a] | Catalyst | NO source | Solvent | Temp. [°C] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $NaNO_2$ | DCE | 90 | – |
| 2 | $RhCl_3$ | $NaNO_2$ | DCE | 90 | – |
| 3 | $NiCl_2$ | $NaNO_2$ | DCE | 90 | – |
| 4 | $Pd(OAc)_2$ | $AgNO_2$ | DCE | 90 | 28 |
| 5 | $Pd(OAc)_2$ | TBN | DCE | 90 | 86 |
| 6 | – | TBN | DCE | 90 | 99 |
| 7[c] | – | TBN | DCE | 90 | 99 |
| 8[c] | – | TBN | $CH_3CN$ | 90 | 87 |
| 9[c] | – | TBN | Acetone | 90 | 79 |
| 10[c] | – | TBN | DMF | 90 | 87 |
| 11[c] | – | TBN | THF | 90 | 89 |
| 12[c] | – | TBN | DME | 90 | 55 |
| 13[c] | – | TBN | Xylene | 90 | Trace |
| 14[c] | – | TBN | Ethanol | 90 | Trace |
| 15[c] | – | TBN | DCE | 25 | N.R. |
| 16[c] | – | TBN | DCE | 70 | 51 |
| 17[c] | – | TBN | DCE | 110 | 99 |

[a] Reaction conditions: **1a** (0.2 mmol), NO source (0.4 mmol), catalyst 10 mol%, solvent (1 mL), 2 h.
[b] Isolated yield.
[c] 30 min.




**Scheme 1** Nitrosylation of imidazo[1,2-*a*]pyridines derivants.

seen from Table 1, good yields could be achieved in $CH_3CN$, acetone, DMF and THF (Table 1, entries 8–11). When DME was used as the solvent, the yield dropped dramatically to 55% (Table 1, entry 12). Moreover, the reaction could hardly be carried out in xylene or ethanol (Table 1, entries 13–14). Using DCE as the chosen solvent, we turned our attention to the influence of temperature on the nitrosylation reaction. No target product could be detected at room temperature (Table 1, entry 15). On raising the temperature, the corresponding yields were also increased with 51% yield obtained at 70 °C (Table 1, entry 16). While further increasing the temperature up to 110 °C, the reaction could still be accomplished in excellent yield (Table 1, entry 17).

To investigate the scope of the protocol, various 2-phenylimidazo[1,2-*a*]pyridine derivatives were employed under the optimized reaction conditions. Encouragingly, most 2-arylimidazo[1,2-*a*]pyridines could be efficiently nitrosylated at the C (3) position (Scheme 1). The corresponding nitrosylation products were isolated in good or excellent yields. 2-arylimidazo[1,2-*a*]pyridines bearing electron-donating groups including Me, OMe, Et, and *t*-Bu, or electron-withdrawing groups, such as F, Cl, Br, $NO_2$, COOMe and $CF_3$ were well tolerated (Scheme 1). Especially, iodine substituent could still stay intact during the nitrosylation reaction rather than a cleave from the imidazo[1,2-*a*]pyridine rings (Scheme 1, **3bd**, **3ge**). Substituents at various positions of the 2-arylimidazo[1,2-*a*] pyridines do not affect the yields significantly. The substituent groups (R1 and R2) could be located at C (6) or C (7) position of imidazo[1,2-*a*]pyridine ring, and at ortho-, meta-, or para-position of the phenyl ring. In order to broaden the substrate varieties, several heterocyclic rings were also investigated and proved to be applicable for the catalytic protocol. (Scheme 1, **3ha**, **3ia**, and **3ja**).

## 4. Conclusions

We have developed an effective method for the nitrosylation of imidazo[1,2-*a*]pyridines in metal free system using TBN as the NO source. Various C-3 nitrosylated imidazo[1,2-*a*]pyridines were obtained in good to excellent yields in 30 min. Meanwhile, the generated products could be used as precursors for multiple transformations. Environmental benignity, functional group tolerance, high efficiency, and straightforward operation make this protocol an effective methodology for industrial applications.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2016.02.004.

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